REMARKS

Applicant respectfully requests reconsideration. Claims 42-71 were previously pending in this application. Claims 44-46, 52-54, and59-61 are withdrawn. Applicants have not canceled the withdrawn claims since they are directed to species. Claim 49 is amended to remove the dependency from the withdrawn claims. Claims 42, 50, 57, 64, and 68 have been amended to add structural detail regarding the CpG oligonucleotides, including structural information, backbone modification and a size limitation. Claims 43, 51, 58, 65, and 69 have been amended to be consistent with the amended independent claim from which they depend. New claims 72-74 are added. As a result, claims 42-43, 47-51, 55-58, 62-71, and 72-78 are still pending for examination with claims 42, 50, 57, 64, and 68 being independent claims. No new matter has been added.

Status of US 09/802,370

Applicant originally filed the instant claims to copy the claims of US 09/802,370. Applicant notes that US 09/802,370 has been abandoned. The only child application appears to be directed to HCV and HBV, according to publicly available databases.

Rejection Under 35 U.S.C. 112

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claim 42-43, 47-51, 55-58 and 62-71 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

On page 4 of the office action the Examiner addresses Applicant's argument related to "functional characteristics." The Examiner states that while "Applicant may assert that Applicant is unaware of one of all of these requirements, these requirements are clearly set forth in MPEP §2163." The Examiner has misunderstood the point Applicant was making in the prior response. In response to a rejection listing points that Applicant's disclosure is purportedly lacking, Applicant argued that there is not a requirement that functional characteristics of a compound be disclosed,

particularly when the structure of a class of compounds is described, along with methods of making and using the molecules. The point is that a description of "functional characteristics" is not a requirement. It is simply an example of factors to look for. In response to Applicant's arguments the Examiner has asserted that "these requirements are clearly set forth in the MPEP." Applicant still disagrees that the MPEP includes a requirement that a specification describe a functional characteristic of a compound in order to meet the written description requirement. It is simply one of several factors. The quoted section of the MPEP states:

> "Whether the specification shows that applicant was in possession of the claimed invention *is not a single, simple determination, but rather is a factual determination reached by considering a number of factors.* Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406." (emphasis added).

Applicant addresses each of these factors listed in the above MPEP section separately:

1. level of skill and knowledge in the art: The level of skill in the art is high. A skilled artisan in the field is an individual with a PhD or MD in the biological sciences, such as immunology or virology.

2. partial structure: The basic structure of oligonucleotides was well known in the art at the time of the invention. Applicant has described a core component of a set of oligonucleotides that is understood to those of ordinary skill in the art, an unmethylated CpG dinucleotide. Applicant discovered that inclusion of an unmethylated CpG dinucleotide in an oligonucleotide resulted in a drug that was capable of causing the body to mount a natural response against invading organisms. It is taught in the specification that the immune reaction to CpG oligonucleotides is believed to be representative of a natural host response

to bacterial infection (paragraph 0145). It was recognized by the inventors that the immune response to CpG motifs is similar to that which occurs in a subject with bacterial infection. Unmethylated CpG motifs are present in bacterial DNA in much higher amounts than in vertebrate DNA. By using synthetic oligonucleotides having unmethylated CpG motifs one can mimic bacterial DNA and stimulate a host response to bacterial infection, thus adding to the natural host response and providing a highly effective response to an invading organism. Numerous publications following Applicant's priority date have described the unmethylated CpG dinucleotide as the essential component of immune stimulatory oligonucleotides. Also it has now been described in publications that CpG oligonucleotides act through a common cellular receptor, TLR9. It is believed that CpG oligonucleotides are recognized by TLR9 and that this leads to the promotion of an immune response in which a Th1 response is favored. It is this common mechanism that unifies the resultant immune response produced by CpG oligonucleotides.

3. physical and/or chemical properties: The specification describes the physical and chemical properties of this class of oligonucleotides. The specification provides a description of the genus of immunostimulatory CpG oligonucleotides, including preferred species and subgenus. (See paragraphs 0055-0060, 0062-0065). The specification also provides representative species of these oligonucleotides, as well as data demonstrating their immunostimulatory activity. (See for example Tables 1-14 and the Examples and accompanying descriptions). The specification also describes backbone modifications (See paragraphs 0071-0073). Thus, the physical and chemical properties of the oligonucleotides are described in the specification.

4. functional characteristics alone or coupled with a known or disclosed correlation between structure and function: The specification describes a class of oligonucleotides having an unmethylated CpG dinucleotide that have a particular function, that is they stimulate an immune response and that this response is useful for the treatment of viral infection. As described above, it is now known that CpG oligonucleotides act through a common receptor, TLR9 to promote this immune response. Applicant describes this

functional property associated with CpG oligonucleotides throughout the specification and at least in paragraph 0014 and 0023.

5. method of making the claimed invention: Methods of making the claimed oligonucleotides are known in the art and are described in the specification. (See paragraph 0167).

Applicants have satisfied each of the factors outlined in this section of the MPEP.

Further, the Examiner has not met the burden of making a *prima facie* case as to why the specification does not adequately support the claims such that it lacks written description. MPEP 2163.04 teaches that:

> "The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). *A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption.* See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97." (emphasis added).

A preponderance of evidence supporting the assertion that a person skilled in the art would not believe that applicant had possession of the claimed invention has not been presented. In fact no evidence has been presented in either Office Action of record to establish that one of skill in the art would not recognize in applicant's disclosure a description of the invention defined by the claims. The rejection consists only of statements directed to the fact that the specification does not show an actual working example of the use of a CpG oligonucleotide in the treatment of a papilloma virus infection and reciting various sections of the MPEP. A lack of a specific working example on the treatment of papilloma virus is not sufficient evidence to establish that one of skill in the art would not recognize Applicant as being in possession of the claimed invention.

On page 7 of the office action the Examiner has restated that "the disclosure fails to provide relevant identifying characteristics relating to the claimed invention. The disclosure fails to set forth

the complete structure of an oligonucleotide that treats, prevents or ameliorate papilloma viral infection."

Applicants maintain that this statement is incorrect. Throughout the specification Applicants teach that the molecule useful according to the methods of the invention is a nucleic acid having an unmethylated CpG dinucleotide. In some preferred embodiments, the unmethylated CpG dinucleotide must have at least 2 nucleotides on the 5' side and the 3' side. In some preferred embodiments the nucleic acid has a stabilized backbone. Examples of numerous CpG containing nucleic acids are shown in the Tables and throughout the description. All of the structure of this class of compounds (oligonucleotides containing an unmethylated CpG dinucleotide) is set forth clearly in the description found in the specification. Applicants have taught in the specification that a class of compounds can be used to treat viral disease. Applicants have fully described the structure of the class of compounds, methods for making the class of compounds, methods for administering the class of compounds and the types of viral disease, including papilloma virus, that could be treated. One of skill in the art would recognize the full scope of the class of compounds useful in the claimed method. The description adequately demonstrates Applicants had possession of the full scope of compounds (oligonucleotides containing an unmethylated CpG dinucleotide) which can be used according to the methods of the invention. It is respectfully requested that the rejection be withdrawn.

Further, Applicants attach herewith several papers published prior to the effective priority date, Woodworth and Simpson (Am. J Path., vol 142 (5): 1544-55 (1993); Schneider (Genitourin. Med., 1993, vol 69 (3): 165-73); and Morris et al (Br J Obstet Gynecol, 1983, vol 90(5):412-20) that demonstrate why one of skill in the art would expect that the change in immune parameters produced by CpG oligonucleotides and described in the specification would be useful in treating papilloma virus infection. Those arguments are set forth in more detail below in the response to the enablement rejection.

Claims 42-43, 47-51, 55-58 and 62-71 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Regarding the enablement rejection, the Examiner asserts that "Applicant has not taught of a single oligonucleotide that is therapeutic against viral infection, including papilloma virus" (page 10). The Examiner further alleges that "Applicant has not taught or provided any guidance directing at the type of immunoparameter that must be modulated, which oligonucleotide has the immunomodulating activity, and the extent in which the modulation must occur to render a therapeutic affect against papilloma virus infection" (page 10). The Examiner goes on to maintain her contention that "Applicant has not provided a single working example that is directed at demonstrating at an oligonucleotide comprising the CpG motif is therapeutic against papilloma virus infection..." (page 12).

MPEP 2164 states that in order to comply with 35 USC 112, it is not necessary to "enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect". An Applicant need not have actually reduced the invention to practice prior to filing and an example may be "working" or "prophetic" (MPEP 2164.02). A prophetic example describes an embodiment of the invention based on predicted results. The lack of working examples should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement.

The Examiner contends that the working examples presented in the application are not commensurate in scope with the claimed invention and do not sufficiently provide a correlation between CpG and its use in treating and preventing viral infectivity.

Applicants disagree and maintain their assertion that, while not actually having treated subjects infected with papilloma virus with the CpG oligonucleotides of the claimed invention, said oligonucleotides induce a pattern of immunostimulation that is consistent with the treatment of viral infection. Further, one of skill in the art, at the time of the invention, would have believed that based on the data and teachings of the specification that one of skill in the art could use CpG oligonucleotides to treat papilloma viral infection.

Applicants disagree with the notion that no facts have been provided to substantiate Applicant's assertion that the observed pattern of immunostimulation is consistent with the treatment of viral infection. Despite having provided such evidence during earlier stages of the prosecution Applicants hereby submit additional evidence to show that the state of the art at the

time the invention was made would have allowed a person of ordinary skill in the art to draw conclusions from the observed pattern of immunostimulation as to the utility of the CpG oligonucleotides to treat viral infection, including papilloma virus.

Applicants have demonstrated that oligonucleotides containing unmethylated CpG motifs are effective in inducing a pattern of immune stimulation that is consistent with the treatment of viral infection. Applicants have provided examples in the specification that show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3, Example 4, Example 11, Figure 6 and Figure 11), and production of IFNγ (Figure 15) as well as other cytokines. On page 53 of the application it states that " in response to unmethylated CpG containing nucleic acid molecules, an increased number of spleen cells secrete IL-6, IL-12, IFN-gamma, IFN-alpha, IFN-beta, IL-1, IL-3, IL-10, TNF-alpha, TNF-beta, GM-CSF, RANTES, and probably others. The increased IL-6 expression was found to occur in B-cells, $CD4^+$ T cells and monocytic cells". This is shown in Examples 2, 3, 4, 11, and Figures 6, 11 and 15.

Woodworth and Simpson (Am. J Path., vol 142 (5): 1544-55 (1993) employed HPV-infected and non-infected cells and analyzed their lymphokine secretion profiles. The authors report that while normal cervical cells constitutively secreted IL-1 alpha, IL-1 beta, IL-1 RA, IL-6, IL-8, TNF-alpha, and GM-CSF, the HPV-infected cell lines "exhibited significant down-regulation of IL-1 beta, IL-6, TNF-alpha, IL-8, and GM-CSF" (page 1548, right column, 1st paragraph, Figure 3, and Table 1). The authors note in their discussion that "if the constitutive release of lymphokines is involved in maintaining normal immunocompetence in the cervical mucosa, then decreased secretion might provide a more favorable environment for persistence of HPV-infected cells" (page 1552, right column, 2nd paragraph). Thus, one skilled in the art would recognize that a drug useful for boosting such cytokines would be useful in the treatment of papilloma virus. Applicant has demonstrated that numerous of these cytokines can be induced.

Consistently, in the abstract of Schneider (Genitourin. Med., 1993, vol 69 (3): 165-73) it is stated that the impaired cellular immune response upon genital HPV infection is characterized by depletion of T helper/inducer cells and/or Langerhans cells and impaired function of natural killer cells and/or the infected keratinocytes. Morris et al (Br J Obstet Gynecol, 1983, vol 90(5):412-20)

studied wart virus infections with no evidence of cervical intraepithelial neoplasia and noted "a patchy reduction or total absence of Langerhans' cells in the epithelium" (page 415, left column, 2nd paragraph). Langerhans' cells are antigen-presenting cells derived from monocytes. There was also a "striking reduction in the number of T lymphocytes". Thus, one of ordinary skill in the art would recognize the therapeutic value of CpG in treating papilloma virus infection.

The relation between IFNγ and treatment of viral infections was studied by Morris et al. (Infection and Immunity, 1982, 35(2):533-536) who showed that IFNγ is produced from two human T-lymphoblastoid lines upon virus infection (see page 536, left column). Baumgarth et al. (Journal of Virology, 1994, 68(11):7575-7581) disclose that IFNγ has been identified as a key factor in immune responses to viral infections and demonstrated IFNγ production in response to influenza virus.

The results obtained by Applicants *in vitro* and *in vivo* (i.e. immune stimulation) are correlated with the specific condition claimed (i.e. viral infection and in particular papilloma viral infection) and the Examiner has failed to provide sufficient evidence that the model does not correlate.

The Examiner has not made a prima facie case of lack of enablement. MPEP § 2164.04 teaches that in "order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, *unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.* Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting

disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370." (emphasis added). In the instant case the Patent Office has not provided a sufficient reason to doubt the objective truth of the statements made in the specification. The only doubt raised related to the lack of an in vivo test of papilloma viral infection and the references cited in support of the unpredictability. Applicant previously addressed each of these references. Thus, a prima facie rejection has not been made.

Regardless, Applicant has presented rebuttal evidence above establishing that the pattern of immune stimulation produced by CpG oligonucleotides is sufficient to establish to one of skill in the art that CpG oligonucleotides could be used to treat papilloma virus. Evidence is provided in the form of publications available prior to the priority date of the invention to establish what one of skill in the art knew at the time of filing of the patent application.

Additionally, Applicant has addressed each of the references cited by the Examiner in support of the lack of predictability of the invention. The Examiner has not addressed any of Applicants arguments about the references specifically. The only reasons for maintaining the rejection in view of these references is found on page 11 and are as follows:

1. "At the time the invention was made, it is well known in the art that the CpG motif present in the oligonucleotide stimulates Th1 immune response, which induces the production of Th1 associated cytokines." This statement is inaccurate. Prior to Applicant's invention it was not known in the art that CpG oligonucleotides were useful for stimulating an immune response. That is the basis of Applicant's invention.

2. "In the instant case, while the claimed invention does not specifically recites the administration of a cytokine, it does relies on the production of a Th1 associated cytokines to render a therapeutic efficacy for a disease. Hence the cytokine art was introduced in the enablement rejections to demonstrate the level of unpredictability and the quantity of experimentation that would be required of the skilled artisan attempting to practice the claimed invention." Applicants disagree. Administration of a cytokine is very different than administering a natural component that induces the body to produce a balanced immune response. A single cytokine may bring benefit

to a subject but it may throw off the balance of other factors leading to problems and side effects. CpG oligonucleotides when administered to the body mimic bacterial infection and cause the body to develop a natural immune response. The issues of enablement for a CpG oligonucleotide and a cytokine are not the same. The specific points are addressed herein.

The Examiner has not addressed the specific points raised by Applicant to rebut each assertion in support of the lack of enablement rejection. Thus Applicant hereby reiterates the entire Wands analysis addressing each of the Examiner's points. It is requested that the rejection either be addressed or withdrawn.

In considering whether a claim is enabled, and whether the amount of experimentation required is undue, there are various factors that the Federal Circuit has said should be considered. In re Wands, 858 F.2d 731, 737, 8 USPQ.2d 1400, 1404 (Fed. Cir. 1988). These include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the level of predictability in the art, and the breadth of the claims. When one considers all of the *Wands* factors, and the full state of the art, it becomes clear that the full scope of the claim is enabled.

Breadth of the Claims

The claims cover the treatment of papilloma virus infection using CpG oligonucleotides. The dependent claims contain additional structural limitations on the CpG oligonucleotide. The CpG must include an unmethylated CpG. In some embodiments the CpG dinucleotide is flanked by specific nucleotides, e.g., a 5' T. In other embodiments multiple CpG dinucleotides are included in the nucleic acid.

Presence or absence of working examples:

The Examiner has stated that the specification does not contain any working examples directed to the claimed invention of use of an oligonucleotide containing the CpG motif in treating, preventing or ameliorating papilloma viral infection. "Nothing exists in the specification demonstrating that fundamental research has been conducted to support Applicants' claim, wherein oligonucleotides comprising the CpG motif treat, present, or ameliorate viral infection including papilloma viral infection."

Applicants have demonstrated that oligonucleotides containing unmethylated CpG motifs are effective in inducing a pattern of immune stimulation that is consistent with the treatment of viral infection. Applicants have provided examples in the specification that show production of antibody in response to oligonucleotide stimulation (Example 2), stimulation of B cells, natural killer (NK) cells and monocytic cells (Example 3, Example 4, Example 11, Figure 6 and Figure 11), and production of IFNγ (Figure 15) as well as other cytokines. The specification asserts that CpG oligonucleotides are useful in treating viral infections, including papilloma viral infections. The combination of the changes in immune parameters demonstrated with CpG oligonucleotides is sufficient to support applicants assertion at the time of the invention that CpG oligonucleotides would be useful in the treatment of papilloma viral infection. Applicants assert that a correlation between CpG and their use in the treatment and/or prevention of viral infection is disclosed and enabled.

Applicants strongly object to the examiner's assertion that "Nothing exists in the specification demonstrating that fundamental research has been conducted to support Applicants' claim". In fact, Applicants specification describes the fundamental research related to the discovery that CpG oligonucleotides are useful in treating viral infection. Many other researchers have begun to work in the field, following Applicants' discovery.

Amount of direction or guidance presented:

Applicants have provided sufficient direction and guidance in the specification. Applicant has described the structural properties of CpG oligonucleotides and have taught that they can be used to treat viral infection including papilloma viral infection. Further Applicants have provided preferred modes of administration and formulations. Those of skill in the art are well aware of such routine methods of formulating and administering drugs.

The Examiner has asserted that "all that is present in the specification are conjectures of potential application of such oligonucleotides". The Examiner's conclusion is inaccurate and unsupported by the evidence. The term "conjecture" is defined in Webster's Ninth New Collegiate dictionary as "a conclusion deduced by surmise or guesswork." One of skill in the art would recognize the utility of treating viral infections was well supported based on the data and description described in the specification. In fact numerous investigators have begun research in the area of

CpG oligonucleotides following the fundamental discovery by the instant inventors that this class of oligonucleotides having a CpG motif were immune stimulatory. The Examiner is requested to provide evidence to support her statement that the claimed invention is based on surmise or guesswork.

Nature of the invention

The invention is directed to a method of treating, preventing or ameliorating papilloma viral infection using a class of CpG containing oligonucleotides having structural requirements. The Examiner has stated that the invention is "directed to the use of the art recognized immunostimulatory activity of oligonucleotides containing the CpG motif." Applicants reiterate on the record, that the discovery that oligonucleotides containing the CpG motif were immunostimulatory and thus useful for treating viral infection, is the invention of Applicants. The invention is not simply a use of some previously discovered art recognized class of compounds known for having a particular activity.

State of the Art

The Examiner has made several statements about the state of the art. In order to address each statement, Applicants have copied the Examiner's statement and provide comments immediately below.

- "The art acknowledges the importance of Th1 type immune response, which is stimulated by the production of Th1 cytokines, in the elimination of intracellular pathogens, including viruses. However, the art has not accredited or recognized any one particular Th1-assoicated cytokine to the treatment, prevention, and amelioration of viral infection in a subject. Specifically, the art teaches that while cytokines secreted by T helper cells are of critical importance for the outcome of many infectious disease, the production of the "right" set of cytokines can be a matter of life or death." (Office Action dated 10/30/06 page 11)
  - The statement is not relevant to the claimed invention. Applicants are not exogenously administering specific cytokines. The claimed invention relates to the delivery of an oligonucleotide which stimulates in vivo the promotion or inhibition of cytokine production. The body decides which cytokines to induce or suppress in response to the administration of the oligonucleotide.

- "Specifically, Infante-Duarte et al. teaches that a tight control over where and when Th1 and Th2 immune responses happen is necessary to keep intracellular infections under control, and to prevent the Th1 type immune response from causing damage to the host. Hence, while the importance of a Th1 type immune response is well recognized in the art, the art further notes that a balance between Th1 and Th2 type immune responses is necessary to resolve an infection." (Office Action dated 10/30/06 page 11-12)
    - This teaching is not inconsistent with the claimed invention. The patent application teaches that CpG oligonucleotides promote an immune response when administered in vivo. The immune response involves a shift in the balance of Th1 and Th2 cytokines such that the Th1 response is favored. The shift is a natural one that occurs in response to a stimulus that Applicants believe a naturally existing stimulant, bacterial DNA. It is believed that CpG containing oligonucleotides mimic bacterial DNA in their ability to promote an immune response. The inventors believed they discovered one of natures pathways fundamental to the immune system. This discovery is described on pages 45-46 of the specification under the heading "Teleological Basis of Immunostimulatory Nucleic Acids." It is taught that the stimulatory CpG motif, identified according to the invention, is common in microbial genomic DNA, but quite rare in vertebrate DNA. Experiments described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrated that the difference in CpG status is the cause of immune stimulation by bacterial DNA. The resultant immune response is a natural one. Not one that is dramatically skewed to cause tissue damage.
- "The cytokine art also provided that the efficacy of Th1 associated cytokines, such as interleukin 2, interleukin 12, and interleukin 18, against intracellular pathogens are controversial, as evidenced by Aoki et al, Bohn et al, Sakao et al, Zaitseva et al and Masihi, K. Aoki et al teaches that while interleukin 2 may confer good protection for non-pathogenic mycobacterial strain Bacille Calmette-Guerin (BCG), interleukin 2 does not confer protection for virulent *M. bovis* infection." (Office Action dated 10/30/06 page 12)

- The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a single cytokine, such as IL-2, IL-12, or IL-18. Additionally, the Aoki et al reference cited by the examiner actually teaches that cytokines have promise in the treatment of infectious disease. On page 231 2nd column it is concluded that "Undoubtedly, in the next several years we may witness the formal introduction of cytokines or their inhibitors to routine clinical use for infectious diseases other than viral hepatitis." and "Cytokines hold great promise to be used as therapeutics or immune adjuvant for vaccination against infectious disease.....Several cytokines have been successfully used for human conditions and it is anticipated that more will enter into clinical applications."

- "Interleukin-12, a Th1 associated cytokine, induces different effector mechanisms that result in either protection or exacerbation of a disease. Specifically, Bohn et al. notes that the administration of exogenous interleukin 12 confers protection against Yersinia enterocolitica in susceptible BALB/c mice, but exacerbates yersiniosis in resistant C57BL/6 mice." (Office Action dated 10/30/06 page 12)
  - Again, the statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine. Additionally, the claimed invention relates to the delivery of an oligonucleotide which stimulates a pattern of cytokine production, not simply a single cytokine such as IL-12.
- "Interleukin 18, a Th1 associated cytokine, is responsible for the progression of endotoxin-induced liver injury in mice primed with interleukin 18." (Office Action dated 10/30/06 page 12-13)
  - The statement is not relevant to the claimed invention. Applicants are not directly administering IL18. Administering a compound is very different than stimulating the body to produce the compound endogenously.
- "Both Interleukin 6 and interferon gamma augment the susceptibility of monocyte-derived macrophages to infection." (Office Action dated 10/30/06 page 13)

- The statement is not relevant to the claimed invention. Applicants are not directly administering IL6 and IFN-gamma. Administering a compound is very different than stimulating the body to produce the compound endogenously.

- "Interleukin 2 increases the production of HIV in vitro, and enhances the translocation of bacteria from intestines to other organs in animal studies." (Office Action dated 10/30/06 page 13, citing Masihi)
  - The statement is not relevant to the claimed invention. Applicants are not directly administering a cytokine and are not treating HIV Administering a compound is very different than stimulating the body to produce the compound endogenously. This point is clarified in the Masihi reference itself. In his review article Masihi describes several classes of molecules and how they are used for fighting infection. One section (section 3) is on the exogenous administration of cytokines as therapeutic agents. This is the section cited by the Examiner which describes some of the troubles associated with exogenous administration of cytokines. The next section (section 4) describes synthetic and natural immunomodulators. Section 4.1 is dedicated to CpG oligonucleotides. Unlike all of the problems highlighted by Masihi related to cytokines, Masihi describes studies in which CpG ODN were demonstrated to protect against *Listeria moncytogenes* and *Francisella tularensis* in mice. Additionally studies are described relating to successful protection against *Trypansoma Cruzi* and *Leishmania major*. The author even concludes "CpG-ODN were even curative when given after lethal *Leishmania major* infection. (page 647 1st full sentence).

Based on the above assertions, the Examiner concludes that "the art teaches that cytokines can be inherently toxic, have unclear pharmacological behavior, and also have pleiotropic effects. Hence, the art recognizes that the use of cytokine to direct treatment is unpredictable and complicated" (Office Action dated 10/30/06 page 13) None of the above-statements support the above conclusions. In each instance but one (the one referring to Infante-Duarte et al.) the Examiner is describing a system of one or more exogenously administered cytokines. Applicants

have not claimed the administration of cytokines. Applicants claims are directed to the administration of oligonucleotides which produce a shift in the balance of cytokine production and cellular activation in a natural environment. The body controls how much of a particular cytokine to produce. The effect is different from administering cytokines. The ability to stimulate an immune response without directly administering immune factors such as cytokines is an advantage of the invention. The teachings of Infante-Duarte et al. cited by the Examiner are not inconsistent with the claimed invention and also don't support the above-conclusion.

Additionally, the Examiner has cited several teachings in the CpG art. Applicants address each of these below.

- "The recognition of the CpG motifs requires Toll-like receptor (TLR) 9, wherein cells that express TLR-9 produce Th1 associated cytokines. However, Mutwiri et al provides that TLR-9 has only been identified in mice and humans. Mutwiri et al also provides that the TLR-9 is differentially expressed in humans and mice. Hence, if the recognition of the CpG motif were dependent of TLR-9 then it would logically follows that the extent of the Th1 type immune response induced by the oligonucleotide would necessarily vary from one species to the next." (Office Action dated 10/30/06 page 14-15, citing Mutwiri et al)
    - Mutwiri et al actually state "TLR9 has yet to be identified in species other than human and mice, *but it is assumed that a similar signaling mechanism is involved in other species*". (Emphasis added) The Examiner's conclusion that the absence of TLR9 in some species would lead to variability in results is misplaced. The reference does not teach that TLR9 is absent is some species. Additionally the reference is a review article describing studies that have examined the effects of CpG therapies in a variety of animals, including mice, humans, cattle, sheep, pigs, horses, goats, rabbits, fish, dogs, cats, and chickens (see for instance page 90 first full paragraph of left column and first 20 lines of right column). The authors conclude in that paragraph in the right column of page 90 that "Together, these data suggest that in vitro stimulation of cells by CpG motifs is conserved across species, and that the enhanced activity of GACGTT in laboratory animals may be an artificial bias due to inbreeding."

- "Each oligonucleotide containing the CpG motif must be considered as a separate agent because the quality and type of immune stimulation induced by these oligonucleotides varies. Krieg et al particularly notes that the type of cytokine stimulation stimulated by oligonucleotides containing CpG motifs is distinct from one oligonucleotide to the next. Additionally, both Krieg et al and Mutwiri et al note that the level and type of immune stimulation varies depending on i) the specific nucleic acids, purines and pyrimidines, surrounding the CpG motif, ii) the spacings between CpG motifs iii) the numbers of CpG motifs in an oligonucleotide; iv) the absence or presence of a CpG motif to the end of the oligonucleotide; and v) the context in which the CpG motif is presented in the sequence." (Office Action dated 10/30/06 page 13-14)

  - Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification and their ability to produce a Th1 favored immune response and be used to treat disease is not only described (e.g., see page 8, lines 9-14 and page 55-56) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention. The fact that there is some variability in the responses depending on the sequence of the oligonucleotide is not surprising. If one were proceeding in a clinical trial one would have to select a single oligonucleotide to use. However, this is not the standard for enablement. Variability with drugs in humans is not unusual. Humans are an outbred population, genetically diverse, and humans respond with great variability to drugs. This is particularly the case where the immune system is involved. Humans have an immune status that fluctuates much more than the mice used in experimental research. A human's immune status on any particular day can determine the human's response to a drug.

- "The CpG art further teaches that the immunostimulatory activity of oligonucleotides containing the CpG is species specific, as evidenced by Mutwiri et al. Table 1 of Mutwiri et al. provides that the *in vitro* immunostimulatory activity of oligonucleotides containing the CpG motif varies from one species to the next. Mutwiri et al. also notes that the level of immunostimulating induced by a particular oligonucleotide is also dependent on the sequence(s) flanking the CpG motif. Specifically Mutwiri et al, notes that the GTCGTT motif, which is the optimal motif for humans, is optimal for stimulation of lymphocyte proliferation in several species including cattle, sheep, goats, horses, pigs, dogs, cats and chickens; whereas the murine CpG motif (GACGTT) is only optimal for inbred rabbits and mice." (Office Action dated 10/30/06 page 14, citing Mutwiri et al)
  - The statement does not provide support for lack of enablement. Simply because one embodiment might be optimal or preferred does not make other embodiments non-enabled. Additionally, the statement taken from Mutwiri et al reflects the analysis of data from several published articles. It does not purport to analyze each and every CpG ODN.
- "The in vitro immunostimulatory activity of oligonucleotides containing the CpG is very species specific." (Office Action dated 10/30/06 page 14, citing Mutwiri et al)
  - As described above, variability is expected. However, it has been described in the specification and confirmed in numerous references that CpG containing oligonucleotides stimulate an immune response. The consistent effect is attributed to the presence of the unmethylated CpG motif in the oligonucleotide.

The Examiner has also recited teachings from Equils and Agrawal relating to the use of CpG treatment for HIV infection. Equils describes a research study in which increased HIV replication was observed in mouse spleen cells treated with CpG ODN. Agrawal is a comment on the Equils article and is followed by a reply by Equils. The last sentence of Equils reply provides a succinct summary of the state of the art at the time of these discussions. "However the biological significance of these transient increases in HIV replication is yet to be determined." The observation by Equils (and limitations of those observations in terms of dosages and timing as described by Agrawal) are preliminary and do not rule out the use of CpG in the treatment of HIV

infection. Additionally, the instant claims are directed to a method of treating papilloma virus infection, not HIV. Such post-filing references do not establish a lack of enablement.

Olbrich et al was cited for the teaching that CpG treatment "accelerated and increased the severity of Friend retrovirus in mice." (Office Action dated 10/30/06 page 15). Olbrich discovered that the timing of administration of the CpG oligonucleotides was an important factor in determining the results of the treatment with CpG for retrovirus infection. Olbrich et al reported that pretreatment with CpG ODN did not induce resistance to type C retrovirus challenge, in contrast to other reports that pretreatment with CpG did induce resistance to challenge with tumor cells, Leishmania, and HSV (page 10662, 1st column). Optimization of timing protocols is expected. It does not undermine the fundamental discovery made by Applicants that CpG ODN are useful for treating infectious disease. Some inoperative embodiments are allowed within a claim. In fact Olbrich et al concluded in the last sentence of the paper that "If used under the right conditions, CpG-ODN should be a powerful substance for antiviral therapy in the future." Again the instant claimed invention is directed to the treatment of papilloma virus infection.

Thus, none of the references or passages cited by the Examiner support a conclusion of the lack of enablement of the claimed invention.

Predictability or unpredictability of the art:

The Examiner has concluded that use of cytokines and oligonucleotides containing CpG motifs in the treatment of viral disease is unpredictable. Applicants disagree. Applicants have addressed each statement by the Examiner from the prior art which was put forth to support this conclusion of lack of predictability. The variability observed with CpG oligonucleotides is not sufficient to demonstrate unpredictability. It simply shows that some oligonucleotides work better than others at stimulating the immune response. Applicants have identified the key structural property, the unmethylated CpG dinucleotide, that allows this class of oligonucleotides to function through TLR9 to stimulate an immune response that is useful in the treatment of viral infection.

Quantity of experimentation necessary:

The Examiner has provided several reasons for why additional experimentation would be necessary. For instance it is stated in the Office Action that "Applicant has not provided much, if any, guidance or direction relating to the claimed invention." It is unclear how this translates to a finding of extensive experimentation. Applicants have taught how to make the CpG ODNs using routine methods known in the art. Applicants have also taught that they produce a pattern of immune stimulation and that they can be administered for the treatment of viral infection. One of skill in the art would simply need to make the ODN or buy it and administer it to a subject having a papilloma viral infection. The skilled artisan would know the best routes of administration to use depending on the subject. The issue of whether a drug is safe and effective in humans such that it should be approved for the use of treating humans is for the FDA to decide, not the Patent Office.

The Examiner has also stated "All that Applicant has provided is a conclusion that is made on the basis of generalized concepts that are well known in the art." The Examiner is requested to provide a basis for this assertion. Which "generalized concepts that are well known in the art" have Applicants used to base their invention on? If the Examiner is referring to the "art recognized" use of CpG oligonucleotides for stimulating an immune response, such an assertion is misplaced. This is the basis of the invention claimed herein. It is not an art recognized concept. If the Examiner is referring to something else, she should provide details. Applicants cannot find any mention of generalized concepts well known in the art described in this office action that would support such a conclusion.

Further, the Examiner has stated "And the formation of a conclusion based on generalized concepts renders the conclusion flawed." (Office Action dated 10/30/06 page 17) It is not clear to the Applicants, what this statement means. As far as Applicant can tell, not only is this statement irrelevant, it is incorrect.

In view of the teaching of the instant application and the state of the art at the time of filing, Applicants submit that the claimed invention can be practiced without undue experimentation. Applicants have provided CpG oligonucleotide sequences that stimulate an immune response (and demonstrated a number of immune parameters *in vivo* and *in vitro*) and have provided guidance to one of ordinary skill in the art to use the CpG oligonucleotides to treat or prevent a viral infection. Based on the teachings in the specification one skilled in the art would have predicted that CpG is

capable of treating viral infection. Numerous references, including those cited by the Examiner, have shown that CpG oligonucleotides can overcome infection, suggesting that CpG ODN is effective in treating viral infection. Therefore, the amount of experimentation required to practice the invention is not undue.

Accordingly, withdrawal of the rejection of claims 42-43, 47-51, 55-58 and 62-71 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Double Patenting Rejection

Claims 42-43, 47-51, 55-58 and 62-71 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 97, of copending Application No. 10/613524. Applicant notes that claim 97 of US 10/613524 has been withdrawn pursuant to a restriction requirement and will be canceled. It is believed that the rejection is moot.

Claims 42-43, 47-51, 55-58 and 62-71 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 37, of copending Application No. 10/894862. Applicant notes that claim 37 of US 10/894862 has been withdrawn pursuant to a restriction requirement and will be canceled. It is believed that the rejection is moot.

Claims 42-43, 47-51, 55-58 and 62-71 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19, of copending Application No. 10/987146.

Claims 42-43, 47-51, 55-58 and 62-71 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 42, of copending Application No. 10/382822.

Applicants elect to defer substantive rebuttal of the rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending Application Nos. 10/987146 and 10/382822 until such time as the cited applications are allowed. Applicant understands that procedurally, in accordance with Section 804 of the MPEP, a "provisional" double patenting rejection will continue to be made by the Examiner in each case until the "provisional" double patenting rejection is the only rejection remaining in one of the applications. Should the pending claims in the cited co-pending Applications be found to be allowable and Applicants are

unable to overcome any remaining provisional obvious-type double patenting rejections in the instant case, Applicants will consider filing a terminal disclaimer in the instant case to overcome the rejection.

Claims 42-43, 47-51, 55-58 and 62-71 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 59, of copending Application No. 11/255100.

Claims 42-43, 47-51, 55-58 and 62-71 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 45, of copending Application No. 11/361313.

Applicants elect to defer substantive rebuttal of the rejection on the ground of nonstatutory obviousness-type double patenting as being unpatentable over copending Application Nos. 11/255100 and 11/361313 until such time as the cited applications are allowed. Applicant understands that procedurally, in accordance with Section 804 of the MPEP, a "provisional" double patenting rejection will continue to be made by the Examiner in each case until the "provisional" double patenting rejection is the only rejection remaining in one of the applications. The patent office should allow the earlier filed application. the instant application to issue as a patent.

Applicant notes that each of US 10/627,331, 10/382,822, 10/306,522, 10/627,413, 10/187,489, 10/649,584, 10788,199, 10/788,191, 10/987,146 is co-owned and includes claims directed to various methods of treating viral infection. Applicant has noticed that the double patenting rejections between the cases are inconsistent and would like to ensure that the Examiner is aware of the co-pending commonly owned patent applications as well as the discrepancy in double patenting rejections.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Dated: October 31, 2007

Respectfully submitted,

By _____

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